Oral Presentations

AUTOLOGOUS TRANSPLANTS

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MGMT-TRANSDUCED γδ T CELLS FUNCTION IN THE PRESENCE OF TEMOZOLAMIDE AND SHOW ENHANCED CYTOTOXICITY AGAINST TEMOZOLOMIDE-RESISTANT HIGH GRADE GLIOMA CELL LINES: POTENTIAL STRATEGIES FOR COMBINATION OF CHEMOTHERAPY AND IMMUNOTHERAPY

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Treatment strategies for high-grade primary brain tumors such as glioblastoma multiforme (GBM) have failed to significantly and consistently extend survival. Recently, several studies have suggested that chemotherapy-induced tumor stress may increase tumor vulnerability to the immune reaponse. We have previously shown that expanded/activated γδ T cells from healthy donors recognize NKG2D ligands expressed on malignant glioma and are cytotoxic to glioma cell lines, primary GBM explants, and human glioma intracranial cell line xenografts placed in immunodeficient mice. In this report, we show standard therapies for GBM based on temozolomide (TMZ) increase the expression of stress-associated NKG2D ligands on TMZ-resistant glioma cells, potentially rendering them vulnerable to attack by γδ T cells. As TMZ is also highly toxic to γδ T cells, we genetically modified γδ T cells in culture using a lentiviral vector encoding P140KMGMT, resulting in resistance to TMZ at concentrations up to 400μM. Genetic modification of γδ T cells did not alter their phenotype or their ability to kill targets, as both non-modified and gene-modified γδ T cells were highly cytotoxic to U87 cells and TMZ-resistant clones of SNB-19 (SNB-19^{TMZ-R}) and U373 (U373^{TMZ-R}) glioma cell lines in the presence of up to 400 μM TMZ. Importantly, gene modified γδ T cells showed greater cytotoxicity to both U373^{TMZ-R} and SNB-19^{TMZ-R} cultures in the presence of TMZ, suggesting that TMZ exposed more targets to γδ T cell lysis. These findings demonstrate that TMZ resistant γδ T cells can be generated without impairing cellular functions, and the genetically modified cells efficiently kill TMZ-resistant human glioma cell lines in the presence of high concentrations of TMZ. These results provide a mechanistic basis for combining and timing chemotherapy and drug resistant cellular immunotherapy to treat GBM.

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PHASE I/II STUDY OF INTRAVENOUS PLERIXAFOR ADDED TO A MOBILIZATION REGIMEN OF G-CSF IN LYMPHOMA PATIENTS UNDERGOING AUTOLOGOUS STEM CELL COLLECTION

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Background: In Phase II and III trials, plerixafor has been combined with G-CSF and administered as a subcutaneous injection of 0.24 mg/kg, given 9-11 hours before pheresis. Intravenous (IV) administration of plerixafor may result in a faster rise and higher peak in the peripheral CD34+ cell count, allowing administration of plerixafor the same day as pheresis and improving stem cell collection.
Methods: The primary objectives of this Phase I/II study were to determine the MTD of IV plerixafor, up to 0.40 mg/kg combined with G-CSF, and the efficacy of IV plerixafor + G-CSF to mobilize ≥ 2 x 10^6 CD34+ cells/kg from pts. with lymphoma. Pts. started mobilization with G-CSF (10 ug/kg SC daily) on days -4 thru -1 and on each day of pheresis (up to 4 pheresis days). IV plerixafor was given over 30 min. 4 hrs. before each pheresis, beginning day 0.
Results: 46 pts. (median age, 53; 31 NHL/15 HL) have been treated to date. In Phase I, 25 pts. were treated with IV plerixafor at escalating doses (10 pts. at 0.16 mg/kg, 3 at 0.24 mg/kg, 6 at 0.32 mg/kg, and 6 at 0.40 mg/kg). One dose-limiting toxicity (grade 2 chest pain) was observed at 0.32 mg/kg. In Phase II, an additional 21 pts. have been treated at 0.40 mg/kg. No grade 3/4 toxicities attributed to plerixafor occurred in any pt. treated at 0.40 mg/kg. Overall, 44 of 46 pts. (96%, 80% CI 89-99%) met the goal collection of ≥ 2.0 x 10^6 CD34+ cells/kg, and 37 of 46 pts. (80%, 80% CI 71-88%) collected ≥ 5.0 x 10^6 CD34+ cells/kg, in a median 2 days of pheresis. 20 of 27 pts. (74%, 80% CI 60-85%) treated with 0.40 mg/kg collected ≥ 2.0 x 10^6 CD34+ cells/kg in 1 day of pheresis. In transplanted pts., there has been no delay in engraftment. Analysis of CD34$^+$ hematopoietic stem and progenitor cells (HSPCs) revealed that G-CSF mobilized grafts were enriched with CD45RA$^-$CD123$^{+/-}$ primitive HSPCs while plerixafor preferentially mobilized CD34^{dim}CD45RA$^+$CD123^{hi} plasmacytoid dendritic cell precursors and CD34$^+$CD45RA$^-$CD123^{hi} cells. Flow cytometric analyses showed that the CD34$^+$ subsets preferentially mobilized by plerixafor expressed high levels of cell surface CXCR4.
Conclusions: Plerixafor IV, at doses up to 0.40 mg/kg, is well-tolerated and effective when added to G-CSF for the mobilization of stem cells from pts. with lymphoma, with mobilization kinetics and stem cell collections that compare favorably with sc dosing. In addition, our data suggest that G-CSF and plerixafor mobilize distinct subsets of human CD34$^+$ HSPCs.

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COMPLEX KARYOTYPE (CK) IS ASSOCIATED WITH INCREASED CUMULATIVE INCIDENCE OF RELAPSE (CIR) FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) FOR MANTLE CELL LYMPHOMA (MCL) IN FIRST REMISSION

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Introduction: Complex cytogenetics predict patient outcomes and response to therapy in many hematologic malignancies, but there are few data regarding their significance in patients undergoing ASCT in MCL.
Methods: Patients undergoing ASCT for MCL at the Ohio State University in first remission with ≥ 3 chromosomal abnormalities were considered complex. Cumulative incidence of relapse (CIR) was measured from the date of transplant until the date of relapse, censoring relapse-free patients at last follow-up. Death without relapse (n = 1) was treated as a competing risk event. Gray's test was used to evaluate differences in CIR.
Results: Of 37 patients, 78% were male. At diagnosis, median age was 60 (range 37 to 74), 89% had bone marrow involvement, and all were stage IV. The median MIPI was 5.9 (range 4.8 to 8.1). Induction regimens included R-M-CHOP (n = 27), R-CHOP (n = 8), and R-HyperCVAD (n = 2). Mobilization regimens included etoposide, cytarabine, rituximab (EAR) (n = 28), GCSF (n = 2), GCSF with plerixafor (n = 4), cyclophosphamide (n = 2), and etoposide (n = 1). Conditioning regimens included BEAM (n = 17), BEC (n = 19), and busulfan, cyclophosphamide, and etoposide (n = 1). Thirteen patients had complex cytogenetics (35%), including 4 with deletion of 17p. Complex patients were more likely to have an ECOG PS ≥ 2 (p = 0.03), and higher median LDH at diagnosis (p = 0.01), with no large differences in MIPI, age, sex, induction regimen, and response to induction (p>0.20). Complex patients had a median time to relapse of 14.8 months versus median not reached in the non-complex group (HR 8.30, 95% CI 2.24 – 30.80, p = 0.002). 3 of 4 complex patients with deletion 17p relapsed within 15 months with 1 death at 5 months, but the time to relapse was still shorter in remaining complex patients (p = 0.01). The induction regimen R-M-CHOP largely coincided with EAR and was associated with longer CIR (p = 0.007) while response, MIPI, conditioning regimen, age, sex, performance status, and LDH were not (p>0.20).
Conclusion: A complex karyotype predicts for a shorter time to relapse in MCL patients undergoing ASCT in first remission. In addition, patients who received R-M-CHOP (all but 1 mobilized with EAR) had prolonged time to relapse. Although complex patients